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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,038	07/28/2005	Harold C Smith	21108.0034U2	6473

23859 7590 02/15/2008

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EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	PAPER NUMBER
1648	

MAIL DATE	DELIVERY MODE
02/15/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/523,038	SMITH ET AL.	
	Examiner	Art Unit	
	LOUISE HUMPHREY	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-124* is/are pending in the application.

4a) Of the above claim(s) *1-97,111-117 and 121-124* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *98-110 and 118-120* is/are rejected.

7)☒ Claim(s) *98,105 and 118* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/8/05, 2/8/07, 8/6/007, 1/4/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Office acknowledges the receipt of Applicant's election and Amendment, filed on 03 December 2007.

Election/Restriction

Applicant elects Group X, claims 98-110 and 118-120, with traverse. The traversal is on the grounds that there is no search burden in examining the entire application and that the cited publications, Yang *et al.* and Schwarze *et al.*, fail to make obvious the technical feature of a chimeric protein comprising a protein transduction domain and an RNA-editing deaminase. Applicant's traversal is unpersuasive for the following reasons:

Each Group is drawn to an invention with different limitations that require a separate search. For instance, the search of a CEM15 mimetic in Group III is not coextensive with the search of an anchor oligonucleotide in Group II and pose a serious search burden. While a search of the prior art for one Group may overlap with that of another group, the searches are not co-extensive and thus would be an undue burden on Office resources. A heavy search burden exists for searching each group of invention as the art relating to the products in Group I-III, VI and VIII will not necessarily provide any information regarding the methods in Group IV, V, VII and IX-XI, while such methods will not necessarily provide any structural information pertaining to the all of the products encompassed by the claims in Group I-III, VI and VIII.

Yang *et al.* disclose an APOBEC-1 protein but do not disclose a protein transduction domain. However, Schwarze *et al.* disclose a Tat peptide that translocates β-galactosidase into cells. It would be obvious to one skilled in the art to modify the APOBEC-1 protein of Yang *et al.* by adding a Tat peptide to transport the cargo protein into the cell, as taught by Schwarze *et al.* to increase the cellular uptake of APOBEC-1. Applicants assert that one would not have imagined that Tat fused to APOBEC-1 would be able to enter a cell but do not state the reason why one would not reasonably expect Tat-APOBEC-1 to enter a cell. Schwarze *et al.* clearly disclose protein transduction domains (PTD) that can traverse biological membranes efficiently, that all cell types appear transducible, and that PTD fusion proteins exhibit delivery of active enzymes to all tissues. The motivation is immediately apparent from the teachings of the references. Therefore, the technical feature is not a contribution over the art, and thus, the claimed inventions cannot be said to have unity of invention.

The restriction among the different products that may be used in the different methods is maintained.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-124 are pending. Claims 1-97, 111-117 and 121-124 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 03 December 2007.

Claims 98-110 and 118-120 are currently examined.

Information Disclosure Statement

Initialed and dated copies of Applicant's IDS form 1449, respectively filed on 08 December 2005, 08 February 2007, 06 August 2007, and 04 January 2008, are attached to the instant Office action.

Claim Objections

Claims 98, 105 and 118 are objected to for depending from a non-elected claim. Appropriate correction is required.

Claim 118 is objected to because the word "is" is missing in front of the phrase "taken up" in line 4.

Claim Rejections - 35 USC § 112, 1st ¶, enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 98-104 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for inducing an immune response comprising contacting a B lymphocyte cell *in vitro* with a chimeric protein comprising activation-induced deaminase (AID), does not reasonably provide enablement for inducing an immune response comprising contacting a B lymphocyte cell in vivo with a chimeric protein comprising activation-induced deaminase (AID), or with any other deaminase

chimera. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 105-110 and 118-120 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors (MPEP §2164.01(a)). See, *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988); and *Ex Parte Forman*, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

Claims 98-103 are drawn to a method of inducing an immune response in response to an antigen in a subject comprising contacting a B lymphocyte cell with a chimeric protein comprising a protein transduction domain and a viral RNA-editing

deaminase, and thereby induce antibody production in the B lymphocyte cell to afford a stronger immune response to an antigen in the subject.

Claims 105-110 are drawn to a method of treating a subject for hyper-IgM syndrome comprising administering to a subject a chimeric protein comprising a protein transduction domain and a viral-RNA editing deaminase, wherein the chimeric protein taken up by B lymphocyte cells induces antibody production sufficient to treat the hyper-IgM syndrome.

Claims 118-120 are drawn to a method of treating a subject for B lymphocyte cell lymphoma comprising administering to a subject a chimeric protein comprising a protein transduction domain and a viral-RNA editing deaminase, wherein the chimeric protein is taken up by cancerous B lymphocyte cells and inhibits blunt cell growth thereof, thereby treating the lymphoma.

The nature of the invention is antibody induction in B cells with a viral RNA-editing deaminase fused to a protein transduction domain. The claims encompass all kinds of immune responses to any antigen and all viral RNA-editing deaminase including CEM15, APOBEC3G, APOBEC1, ADAR1 and ADAR2. The breadth of the claimed invention is exceedingly large and fails to receive adequate support in the specification. The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

Working examples. The disclosure fails to provide any working embodiments that meet the claimed limitations. While there are examples that characterize the structures and functions of various deaminases, namely CEM15, ARP1, Cdd1, AID,

APOBEC1 and its related proteins by structural comparison and activity assays and methods for identifying inhibitors, they do not relate to contacting B lymphocytes *in vitro* or *in vivo* and measuring the amount of immune response in the B cells, let alone the treatment of hyper-IgM syndrome and B cell lymphoma. No *in vivo* working example of B cell contacting is disclosed in the specification.

Guidance in the specification. The specification provides little guidance regarding practice of the claimed methods. 1) One skilled in the art is left with no guidance on how to target the chimeric protein to only B lymphocyte cells in the subject body. 2) The disclosure fails to provide sufficient guidance pertaining to the mechanisms in the treatment of hyper-IgM syndrome or B cell lymphoma. The specification does not disclose the effect, if any, of the deaminase-contacted B lymphocyte cells in a diseased or normal model. 3) The disclosure also fails to provide any guidance pertaining to the molecular determinants of a viral RNA-editing deaminase that are involved in induction of immune response, which might enable the skilled artisan rationally identify the deaminases that function in the claimed manner. However, without sufficient guidance pertaining to a suitable molecular target, the skilled artisan has only been extended an undue invitation to further experimentation to ascertain or identify which deaminases might function in the desired manner. 4) Furthermore, there is no teaching of the specificity, type, and duration of the immune response.

State of the prior art. The prior art is unpredictable and fails to provide sufficient illumination pertaining to the structural constraints governing B-cell targeted delivery of AID and the mechanisms underlying the treatment of the hyper-IgM

syndrome and the inhibition of blunt cell growth in B cell lymphoma. However, no such guidance is available in the specification for the current genus of viral-RNA editing deaminases. The only deaminase known to induce antibody protein production in B lymphocyte cells *in vitro* by involving in the somatic hypermutation of the variable regions in the immunoglobulins is activation-induced cytidine deaminase (AID) (Martin *et al.*, 2002).

Amount of experimentation necessary. "Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See *Fields v. Conover*, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). The disclosure fails to provide sufficient working embodiments to enable the breadth of the claimed invention. Legal precedence dictates that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification. *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18 24 (C.C.P.A. 1970). *In re Vaeck*, 20 U.S.P.Q.2d 1438 (C.A.F.C 1991). *In re Angstadt*, 537 F.2d 498, 502-03, 190 U.S.P.Q. 214, 21 (C.C.P.A. 1976). In regards to the deaminase, this is pure speculation on Applicant's part that the all viral-RNA editing deaminases can treat any somatic hypermutation disorder like hyper-IgM syndrome and B lymphocyte cell lymphoma in humans given that the state of the art of "deaminase-induced B cell therapy" is undeveloped. There is no specific guidance in the art or specification and no specific examples of treatment set forth in the specification. While Applicant is not required to set forth working examples, the specification must set forth sufficient teachings to allow one to practice the claimed invention. There is no evidence that the viral-deaminases encompassed by the claimed

method will actually be suitable for treating diseases. When all the aforementioned factors are considered *in toto*, it would clearly require undue and unpredictable experimentation from the skilled artisan to practice the claimed invention.

Thus, the instant invention, based on the evidence as a whole, in light of the factors articulated by the court in *In re Wands*, lacks an enabling disclosure.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 98, 99 and 101-104 are rejected under 35 U.S.C. §103(a) as being unpatentable over Martin *et al.* (2002, No. A227 in the IDS filed on 08 December 2005) in view of Schwarze *et al.* (2000, No. A305 in the IDS filed on 08 December 2005) and Sutkowski *et al.* (1994).

The instant claims are drawn to a method of inducing an immune response in response to an antigen in a subject comprising contacting a B lymphocyte cell *in vitro* with a chimeric protein comprising a protein transduction domain and a viral RNA-editing deaminase, and thereby induce antibody production in the B lymphocyte cell to afford a stronger immune response to an antigen in the subject. Claim 104 further limits the viral RNA-editing deaminase to human activation-induced cytidine deaminase (AID).

Martin *et al.* disclose contacting three human B cell lines, Ramos, BL-2 and CL-01, respectively, with vectors expressing human activation-induced cytidine deaminase (AID). AIDS is expressed specifically in germinal-center centroblasts of a B lymphocyte cell during B cell differentiation and is required for somatic hypermutation of the immunoglobulin variable region genes, the process which produces high affinity protective antibodies. See page 802, 2nd column. Martin *et al.* disclose that hybridomas (antigen-challenged B cells fused with myeloma tumor cells that can grow indefinitely in culture) can be induced to undergo high rates of somatic hypermutation with expression of AID to obtain subclones that produce high-affinity monoclonal antibodies and/or antibodies that are more specific. See page 805, 1st column, first full paragraph.

Martin *et al.* do not disclose contacting a B lymphocyte cell with the chimeric protein comprising a viral RNA-editing deaminase and a protein transduction domain.

Schwarze *et al.* suggest covalently tethering pharmacological proteins, compounds, or DNA to protein transduction domains (PTD), which possess the ability to cross the lipid bilayer of cells in a concentration-dependent manner, to deliver these molecules to all cells *in vivo*. See page 45, the sentence bridging the 1st and the 2nd column. Schwarze *et al.* specifically disclose the Tat transduction domain. See page 45, 3rd column, and Figure 1. Schwarze *et al.* specifically disclose protocols for Tat fusion proteins to transduce into cells and yield biological activity. See page 46, 3rd column.

Neither Martin *et al.* or Schwarze *et al.* disclose introducing the protein-contacted B lymphocyte cells into the subject.

However, Sutkowski *et al.* disclose injecting deaminase-expressing B lymphocyte cells into mice intravenously. See page 8876.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the B cell antibody induction method of Martin *et al.* so as to replace the vector expression of AID with a direct cell delivery by fusing AID with Tat PTD as taught by Schwarze *et al.* The skilled artisan would have been motivated to do so to improve the contact between the B lymphocyte cell and AID. It would also have been obvious to modify the method of Martin *et al.* so as to include a further step to introduce the B lymphocyte cells into the subject after they are contacted with the therapeutic deaminase, as taught by Sutkowski *et al.* There would have been a reasonable expectation of success, given it is known in the art that Tat PTD fusion proteins can transduce different proteins into all cell types and yield biological activity, as taught by Schwarze *et al.*, and given that it is long been known in the art to contact B lymphocyte cells with a therapeutic protein in vitro and subsequently introduce the B cells into the subject, as shown by Sutkowski *et al.* Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Correspondence

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey, Ph.D. whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9:30 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/L. H./
Examiner, Art Unit 1648

/Bruce Campell/
Supervisory Patent Examiner, Art Unit 1648